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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/693,057	Applicant(s) KOLKMAN ET AL.
	Examiner Sue Liu	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 15 August 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 25-41 is/are pending in the application.

4a) Of the above claim(s) 34-41 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date see the attachments.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-24 have been cancelled as filed 4/17/06;

Claims 25-41 are currently pending;

Claims 34-41 have been withdrawn;

Claims 25-33 are being examined in this application.

Election/Restrictions

1. Applicant's election with traverse of Group I invention (Claims 25-33) in the Reply filed on 8/15/06 is acknowledged. The traversal is on the ground(s) that there is no "undue burden" to search all the Groups I-III inventions. This is not found persuasive because the different inventions (Groups I-III) are distinct, and have separate classifications, as discussed in Restriction Requirement mailed 5/18/06, pp. 2-3. These distinct inventions would require different searches in each of the respective classes and/or subclasses. The searches required for each group are not co-extensive thus requiring a burdensome search. Additionally, different patentability considerations are involved for each group. For example, a patentability determination for Group II would involve a determination of the patentability of a library of molecules while a patentability determination for Group I would involve a determination of the patentability of a combination of method steps of identifying multimers that bind a target. These considerations are very different in nature. The different steps of the Group I method would require separate searches, and would not be co-extensive for Group II or III product.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 34-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/15/06.

3. Applicants elected the following species:

A. A single species of a target molecule. Applicants elect "IgE".

B. A single species of a first monomer domain. Applicants elect an "LDL receptor class A monomer domain".

C. A single species of a second monomer domain. Applicants elect an "LDL receptor class A monomer domain".

D. A single species of a third monomer domain. Applicants elect an "LDL receptor class A monomer domain".

in the Reply filed on 8/15/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

4. This application is a CIP of 10/289,660 (filed on 11/06/2002; now ABN), which is a CIP of 10/133,128 (filed 04/26/2002), which claims benefit of the following provisional applications:

60/374,107 04/18/2002;

60/333,359 11/26/2001;

60/337,209 11/19/2001;

60/286,823 04/26/2001.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/286,823, filed on 4/26/01, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The current application obtains the priority date of 60/337,209.

Thus, the <u>effective filing date of the instant application is 11/19/01</u>.

Information Disclosure Statement

6. The information disclosure statement filed 8/16/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent

literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The copies of the cited the foreign patent documents and the non-patent literature publications are not found in the parent case 10/133,128. It has been placed in the application file, but the information referred to therein in regard to the foreign patent documents and the non-patent literature publications has not been considered, as indicated on the attached IDS form.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

For inventor, Per-Ola Freskgard:

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

9. Claims 25-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a method for identifying a multimer that binds to a target molecule, the method comprising, providing a library of polypeptides, the polypeptides comprising different monomer domains, wherein the monomer domains have 30-100 amino acids; screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule; linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the fast monomer domain and one of the plurality of different monomer domains; screening the library of multimers for the ability to bind to the target molecule; and identifying a multimer that specifically binds to the target molecule, wherein the multimer comprises the first monomer domain and a second monomer domain.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims (especially Claim 25) are drawn to a genus of polypeptides comprising a genus of monomers (or monomer domains). The instant claims are also drawn to a genus of multimers that are comprised of the monomers. The instant specification defines the term "monomer domain" or "monomer" broadly to encompass any "discrete region found in a protein or polypeptide" (p. 21 of the spec.). The monomer domains "forms a three-dimensional structure in solution", and can specifically bind to a target molecule (p. 21 of the spec.). The monomer domain can be of any size (p. 32, [133] of the spec.). The instant claim 25 recites "the monomer domains <u>have</u> 30-100 amino acids" (emphasis added), which can be broadly interpreted to mean that each of the monomer domains can have any number of amino acid residues that is above 30. (See MPEP 2111.03 on discussion of "transitional phrases" such as "having".) Thus, any segment of polypeptide or protein with ≥30 amino acid residues that can bind to a target molecule is a "monomer" or a "monomer domain" as defined by the instant specification.

Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of monomers, and the genus of multimers that comprise of any combination of any "monomers". In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genuses of monomers and/or multimers.

The only examples of monomers and/or multimers are the LDL receptor A domain, and specific multimers formed with the LDL A domains (Examples 2-5, and 7-12), and one example of C2 domains (Example 6). Two examples of two types of monomer domains that can be manipulated and formulated into multimer proteins do not constitute a representative number of species of "monomers" and/or "multimers" for the claimed genuses of monomers and/or multimers.

Although the instant specification briefly lists certain known domains in the art as examples of monomers, there is no specific discussion how these domains share common structure/functions. In addition, it has not been demonstrated by the instant disclosure that these protein domains (the purported "monomers") can be linked to other monomers, and to generate multimers that can bind the same target as one of the monomer unit in the multimer.

The state of prior art does not provide teachings of generating any multimers (any protein) from any monomers (e.g. any protein fragments). The state of art, however, does teach that the stability of proteins, especially heterologous proteins (proteins such as the ones of the instant claims), are highly unpredictable and may not be expressed (or made) properly. For example, Roodveldt et al (Current Opinion in Structural Biology. Vol. 15: 50-56; 2005), teach the problems that exist for generating heterologous proteins (e.g. non-natural proteins) such as production of insoluble proteins, and proteins that may be inactive or aggregated (p. 50, left and top of right cols). The Roodveldt reference also teaches that "it is largely unknown, however, how the stability of a protein is encoded in its sequence and how individual amino acid changes contribute to stability". Thus, the stabilities of proteins with various amino acid sequences are highly unpredictable, and hence the success of generating such proteins is also unpredictable.

The recited method of producing multimers that are composed of monomers (i.e. any protein fragments) is essentially a trial and error process that would involve identifying monomers that can be stably generated, and multimers that can be stably generated using the monomers. Without identifying the required monomers that can be used to establish the library of multimers, and without the successful generation of stable multimer proteins, the claimed method of screening the monomers and/or multimers against target molecules cannot be accomplished.

Therefore, applicants are not in possession of the genuses of monomers and/or multimers that can be successfully generated and used to screening for binding of a target molecule. Applicant's claimed broad scope of methods of screening various polypeptides represents only an invitation to experiment regarding possible monomers and/or multimer that may or may not be generated.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Scope of Enablement Rejection

10. Claims 25-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating libraries of monomers and/or multimers based on LDL

receptor A domains alone, and C2 domains alone, does not reasonably provide enablement for generating other proteins that comprise any other monomers and/or multimers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The breadth of the claims seems to encompass any proteins comprising any monomers with any amino acid sequences of >=30 amino acid residues, and any multimers formed from any combination of the monomers. The instant claims (especially Claim 25) are drawn to a genus of polypeptides comprising a genus of monomers (or monomer domains). The instant claims are also drawn to a genus of multimers that are comprised of the monomers. The instant specification defines the term "monomer domain" or "monomer" broadly to encompass any "discrete region found in a protein or polypeptide" (p. 21 of the spec.). The monomer domains

"forms a three-dimensional structure in solution", and can specifically bind to a target molecule (p. 21 of the spec.). The monomer domain can be of any size (p. 32, [133] of the spec.). The instant claim 25 recites "the monomer domains have 30-100 amino acids" (emphasis added), which can be broadly interpreted to mean that each of the monomer domains can have any number of amino acid residues that is above 30. (See MPEP 2111.03 on discussion of "transitional phrases" such as "having".) Thus, any segment of polypeptide or protein with ≥30 amino acid residues that can bind to a target molecule is a "monomer" or a "monomer domain" as defined by the instant specification.

Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of monomers, and the genus of multimers that comprise of any combination of any "monomers". In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genuses of monomers and/or multimers.

The nature of the invention

The nature of the invention is a method of generating and screening libraries of proteins (or polypeptides) that comprise any monomer and/or multimer domains that have any amino acid sequences.

The state of the prior art/ The predictability or lack thereof in the art

The state of prior art does not provide teachings of generating any multimers (any protein) from any monomers (e.g. any protein fragments). The state of art, however, does teach

that the stability of proteins, especially heterologous proteins (proteins such as the ones of the instant claims), are highly unpredictable and may not be expressed (or made) properly. For example, Roodveldt et al (Current Opinion in Structural Biology. Vol. 15: 50-56; 2005), teach the problems exist for generating heterologous proteins (e.g. non-natural proteins) such as production of insoluble proteins, and proteins that may be inactive or aggregated (p. 50, left and top of right cols). The Roodveldt reference also teaches that "it is largely unknown, however, how the stability of a protein is encoded in its sequence and how individual amino acid changes contribute to stability". Thus, the stabilities of proteins with various amino acid sequences are highly unpredictable, and hence the success of generating such proteins is also unpredictable.

Besides the problems with generating stable proteins for using in various methods such as screening, exogenous (e.g. non-natural) proteins production requires considerations in many different areas. For example, Greene (Methods in Molecular Biology. Vol. 267: 3-14; 2004) teaches many potential problems with producing exogenous proteins (Abstract of the reference). Greene teaches problems related in the following areas: "translational compatibility" (p. 4+), "protein folding compatibility" (p. 6+), "protein solubility compatibility" (p. 7+), "posttranslational modification" (p. 8+), etc. Thus, it is highly unpredictable whether a particular exogenous protein can or cannot by properly produced using the known expression systems.

The above discussion only illustrated a few problems with generating stable proteins with any amino acid sequence. Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any monomer and/or multimers with any amino acid sequences.

The level of one of ordinary skill

The level of skill is high.

The amount of direction or guidance present

The only guidance present in the instant specification is directed to LDL receptor A domain and C2 domains as monomers. The only guidance provided for generating multimers are based on either the LDL receptor A domains alone (i.e. the multimers are comprised only of LDL A domains), and C2 domains alone. There is no guidance described for using other "monomers" with other amino acid sequences.

The presence or absence of working examples

The only presence of a working example is the examples listed on pages 93-114 (Examples 1-12) for the generations of LDL receptor A domain multimers and C2 multimers. Because the proteins with different combination of different monomers and/or multimers may or may not be generated, and used for screening against targets, working examples that are structurally or functionally representative of the entire genus of the claimed methods would be required.

The quantity of experimentation needed

Due to the various problems with protein production such as stability, solubility, and proper expression of the protein, it is highly unpredictable to successfully generate proteins with

various monomer and/or multimer domains (with different amino acids). Thus, undue experimentation would be required. The art has not demonstrated all the possible protein monomers, and all possible multimers that can be made from combining the monomers. Because the instant specification only provides guidance for two examples of monomers (LDL receptor A domains and C2 domains), undue experimentation would be required to practice claimed method of screening and generating libraries of proteins comprising any monomers.

Conclusion

Due to the non-routine experimentation necessary to determine the specific methods for screening/generating monomers that are feasible as building blocks for generating multimers, and the feasibility of generating stable multimer proteins; the lack of direction/guidance presented in the specification regarding the specific requirements for the method, and the structural/functional limitations for the claimed "monomer" and "multimer"; the unpredictability of the multimer generation method as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Note: the instant claim numbers are in bold font.)

12. Claims 25, 27, 28, 30, 31, and 33 are rejected under **35 U.S.C. 102(b)** as being anticipated by Barbas et al (US 6,140,466; 10/31/2000).

The instant claims recite a method for identifying a multimer that binds to a target molecule, the method comprising, providing a library of polypeptides, the polypeptides comprising different monomer domains, wherein the monomer domains have 30-100 amino acids; screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule; linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the fast monomer domain and one of the plurality of different monomer domains; screening the library of multimers for the ability to bind to the target molecule; and identifying a multimer that specifically binds to the target molecule, wherein the multimer comprises the first monomer domain and a second monomer domain.

Barbas et al, throughout the patent, teach identifying or generating zinc finger polypeptides (reads on polypeptides comprising monomers and multimers) that bind to specific target nucleotides (Abstract of the reference).

The instant specification defines the term "monomer domain" or "monomer" broadly to encompass any "discrete region found in a protein or polypeptide" that can specifically bind to a target molecule (p. 21 of the spec.), and the monomer domain can be of any size (p. 32, [133]). Thus, any segment of polypeptide or protein that can bind to a target molecule is a "monomer" or a "monomer domain" as defined by the instant specification.

The zinc finger containing proteins taught by Barbas et al have "discrete regions" such as the different zinc finger regions (Figure 8A of Barbas), which either the individual "Fingers" (1-3) or the combination of the "Fingers" is a monomer domain according to the definition of the instant disclosure. The instant specification also discloses "zinc finger" as an example of "monomer" or "monomer domain" (p. 2, [20] of the instant spec.). Thus, the zinc finger regions taught by Barbas et al reads on the monomer domains of 30-100 amino acids of **clm 25**. As indicated by Figure 8 of the Barbas reference, "finger 1" has about 30 amino acids, and the combination of fingers 2 and 3 has about 60 amino acids. Furthermore, the reference also teaches a linker fused two three-finger proteins and multi-finger proteins (Abstract and Example 13 at col. 15, lines 20+ of Barbas), which each of the individual fingers and/or the combination of fingers (such as a two finger domain of about 60 amino acids) read on a monomer domain that has 30-100 amino acids.

Barbas et al also teach generating libraries of zinc finger proteins (through molecular cloning) and screening the libraries of zinc finger protein against nucleic acid target through binding assays (See Examples 1-14, especially, Examples 3 and 13), which reads on the screening of the library of polypeptides for affinity to a target molecule of **clm 25**, and the polynucleotides encoding the polypeptides of **clm 30**.

The reference teaches the generation of phage display library of zinc finger proteins with the size of $5X10^7$ PFU (col. 40, lines 30+), which reads on at least 100 different polypeptides of **clm 31**.

Barbas also teaches randomization of amino acid residues only in the "finger 3" region of the zinc finger protein (Example 3 of Barbas), and thus holding other regions in the protein

constant. The reference also teaches multiple panning procedure comprising several rounds of nucleic acid target recognition and replication (cols. 40-41). These read on linking the first monomer domain to a plurality of different monomer domains, forming multimers, and screening multimers against the target molecule of **clm 25**.

The reference teaches each of the zinc finger of the zinc finger protein contains two cysteine residues (col. 1, lines 43+). The reference also teaches polypeptides comprising multiple "fingers" such as 3-12 fingers (col. 50, lines 30+), and thus a combination of three fingers that constitute as a "monomer" having six cysteines, as recited in **clm 27**.

The reference also teaches improved affinity for binding the target nucleic acid sequence of the mutated zinc finger protein (multimers) (col. 48, lines 32+), which reads on the increased affinity of **clm 28**.

The reference also teaches linking the zinc finger protein (with different numbers of monomers) to other protein domains (such as Jun/Fos leucine zippers and/or additional zinc fingers), and screening against target nucleic acid binding (see Examples 12-14), which reads on the trimers screening of **clm 33**.

13. Claims 25-30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988).

Esser et al, throughout the publication, teach mutational analysis of the ligand binding domain (reading on LDL receptor class A monomer domains of **clm 32**) of the human LDL lipoprotein receptor (see Figure 1), which indicates that each of the cysteine rich repeats of the

LDL receptor has around 40-70 amino acids. The LDL receptor repeats and/or combination of the repeats read on the monomers, and the multimers of **clm 25**, and the trimer of **clm 33**.

The reference also teaches that the LDL receptor binds to various ligands (such as ApoB-100 of LDL and ApoE) through the cysteine-rich repeat regions (corresponding to the LDL receptor class A monomer domains), which reads on the protein target molecule of **clm 25 and 29**.

The reference teaches that the LDL receptor A domains are identified, and different mutations are generated in different A domains (or monomers) that are encoded by polynucleotides (see Figure 1 and p. 13283, right col.), which reads on the linking of an identified monomer with a plurality of different monomers (the repeats with different mutations) to form multimers (such as trimers), and screening for target binding multimers of **clms 25 and 33**, as well as polynucleotides of **clm 30**.

The reference also teaches that mutations in different cysteine-rich sequences (the different monomer domains) lead to different binding specificity to different ligands (see Abstract, Tables I and II, and p. 13287+ of the reference), which reads on the increased binding specificity of **clm 28**.

It is known in the art that the six cysteine residues in each of the cysteine-rich repeats (monomer domains) inherently form disulfide bonds as evidenced by Fass et al (Nature. Vol. 388: 691-693; 1997), and therefore the structure taught by the reference (Esser et al) reads on the disulfide bond and six cysteines of **clms 26 and 27.**

14. Claims 25-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bajari et al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept., 1998).

Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domain (LR8 fragments) or variants thereof that bind to a protein target (see Abstract).

The reference teaches the LR8 fragment of the LDL receptor is the LDL receptor type A domain (p. 379, right col.), which reads on LDL receptor class A monomer domains of **clm 32**. The reference also teaches the LR8 repeats have more than 30 amino acid residues, and have six cysteines (see Figures 1 and 2; p. 1055, left col.). The LR8 repeats and/or combination of the repeats read on the monomers, and the multimers of **clm 25**, the trimer of **clm 33**, and the six cysteines of **clm 27**.

The reference also teaches disulfide bridges (or bonds) formed by the six cysteine residues (p. 1058, right col., middle of para 1), which reads on the disulfide bonds of **clm 26**.

The reference also teaches that the screening (or panning target) is receptor associated protein (RAP) (Abstract and p. 1059, left col., para 2), which reads on the protein target molecule of **clm 25 and 29**.

The reference teaches that the LDL receptor A domains are identified, and different mutations are generated in different A domains (monomers or repeats) that are encoded by polynucleotides (p. 1059, left col.), which reads on the linking of an identified monomer with a plurality of different monomers (the repeats with different random mutations) to form multimers (such as trimers), and screening for target binding multimers of **clms 25 and 33**, as well as polynucleotides of **clm 30**.

The reference also teaches that isolated LR8 domains have high affinity to the ligand (p.1057, right col., and pp. 1055-1056, bridging para), which reads on inherent property of increased binding specificity of the multimers of **clm 28**.

The reference teaches the library has 10^8 phages (containing different polypeptides), and isolation of 120 phage clones (p. 1055, left col.), which reads on the at least 100 different polypeptides of **clm 31**.

15. Claims 25-31 and 33 are rejected under **35 U.S.C. 102(e)** as being anticipated by Etzerodt et al (US 2004/0132094 A1; 7/8/2004; priority date: 2/28/2001).

Etzerodt et al, throughout the publication, teach libraries of proteins that comprise C-type Lectin-like domains, and the methods of generating such libraries (see Abstract of the reference).

The reference teaches the C-type lectin-like domains (CTLDs) has approximately 50 to 70 amino acid residues, as indicated by Table 1 and Figure 1 of the reference (p. 2-3 and [0007]), which the CTLDs read on the monomer domains of **clm 25** as defined by the instant specification (see the discussion above regarding the definition for "monomer").

The reference teaches generating libraries of proteins that comprise mutant CTLDs (p. 18, [0176]+) and screening the library against target molecules ([0188]), which reads on the screening of the library of polypeptides comprising different monomer domains of **clm 25**.

The reference teaches that the protein libraries are generated based on tetranectin CTLD and the tetranectin is trimeric in nature ([0046] and [0192]), and generation and screening of multimeric libraries ([0071])-[0076]; and Claims 1-29; especially Claims 10 and 13), which read on the screening of multimers and trimers of **clms 25 and 33**.

The reference teaches the CTLDs contain six cysteine residues (see Figure 1), and contain two or three intra-chain disulfide bridges (or bonds) ([0004]), which read the disulfide bond of **clm 26** and the six cysteines of **clm 27**.

The reference teaches screening the combinatorial libraries (monomer or multimer libraries) based on affinity selection, and "isolating progressively better binder by repeated rounds of panning and re-amplification (Claim 29 of the reference), which read on the increased affinity of **clm 28**.

The reference teaches the CTLDs (such as tetranectin) bind to various targets including plasminogen, fibrinogen/fibrin, and apolipoprotein, which reads on the target is a protein of **clm 29**.

The reference teaches the libraries of polypeptides are encoded by polynucleotides (Claim 22 of the reference), which reads on the polynucleotides of **clm 30**.

The reference teaches the sizes (such as 10^{11}) of the phage display libraries used to express the libraries of polypeptides ([0225]), which reads on at least 100 different polypeptides of **clm 31**.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari et al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept., 1998).

Esser et al, throughout the publication, teach mutational analysis of the ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor, as discussed above.

Esser et al do not specifically teach the at least 100 different polypeptides comprising the monomers and/or multimers, as recited in **clm 31**.

However, Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domains (LR8 fragments) or variants thereof that bind to a protein target, as discussed above. The reference also teaches the display library contains at least 100 different polypeptides, as discussed above. In addition, the reference teaches the advantages of screening large libraries such as the approach would allow developments of diagnostics and/or therapeutics of interest (Abstract of the Bajari reference). The reference further teaches the screening of phage libraries (containing a large number of polypeptides) would allow isolation of high affinity polypeptides that are in soluble form (p. 1057, last para).

Thus, a person of ordinary skill in the art would have been motivated at the time of the invention to screen large libraries of polypeptides (at least 100 polypeptides) to isolate the

desired polypeptides with high target binding affinity, due to the fact that Bajari teaches the advantages and the need to screen large libraries to isolate polypeptides of interest. A large library contains more diverse polypeptides as taught by Bajari (10^8 phages; p. 1055, left col.), and thus would allow higher probability of success of isolating a desired target.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Bajari et al have demonstrated the success of screening libraries of monomers (LDL receptor A domains) containing at least 100 different polypeptides.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15-17, and 20-26 of copending

Application No. 11/281,256 (20060234299; filed 11/16/05). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '256 application claims a method of identifying a monomer domain (comprising 30-100 amino acids) and multimers that bind to a target (Claims 1, 6 and 20, for examples), and the monomers comprise six cysteines and disulfide bonds (Claims 1 and 3, for examples).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 11/281,245 (20060223114; filed 11/06/2005). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '245 application claims a method of identifying a monomer domain (comprising 30-100 amino acids) and multimers that bind to a target (Claims 1, 6-9 and 18, for examples), and the monomers comprise six cysteines and disulfide bonds (Claims 1 and 3, for examples).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claim 25 and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 207-214 of copending Application No. 10/966,064 (20050221384; filed 10/15/04). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '064 application claims a method of

identifying a monomer domain (comprising 30-100 amino acids) and multimers that bind to a target (Claims 207 and 210).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-32 of copending Application No. 10/971,679 (20050164301; filed 10/22/04). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '679 application claims a method of identifying a monomer domain (comprising 30+ amino acids) and multimers that bind to a target (Claims 21 and 24), for examples), and the monomers comprise six cysteines and disulfide bonds (Claim 21, for example), as well as the LDL receptor A domains (Claim 21).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 21, 29, 33, 36, 78, and 98 of copending Application No. 10/871,602 (20050089932; filed 6/17/04). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '602 application claims a method of identifying a monomer domain (comprising at least 50 amino acids) and multimers that bind to a target (Claims 1, 2 and 11, for examples), and the monomers

comprise six cysteines and disulfide bonds (Claims 11 and 23, for examples), as well as the LDL receptor A domains (Claim 11).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 13, 16, 23, 29, 33, 36, 78, and 98 of copending Application No. 10/840,723 (20050053973; filed 5/5/2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '723 application claims a method of identifying a monomer domain (comprising at least 50 amino acids) and multimers that bind to a target (Claims 1, 2 and 11, for examples), and the monomers comprise six cysteines and disulfide bonds (Claims 11 and 23, for examples), as well as the LDL receptor A domains (Claim 11).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claim 25, 26, and 28-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18, 21-24, 29-31 and 34-36 of copending Application No. 10/957,351 (20060008844; filed 1/12/2006). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '351 application claims a method of identifying a monomer domain (comprising at least 35 amino acids) and multimers that bind to a target (Claims 18, 22 and 29, for examples), and the

monomers comprise disulfide bonds (Claims 30-31, for examples), as well as the LDL receptor A domains (Claim 34).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claim 25-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 18-21, and 24-27 of copending Application No. 11/155,989 (20060177831; filed 6/17/05). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '989 application claims a method of identifying a monomer domain (comprising 30-100 amino acids) and multimers that bind to a target (Claims 15 and 19, for examples), and the monomers comprise six cysteines and disulfide bonds (Claims 15, 18, and 25, for examples), as well as the LDL receptor A domains (Claim 26).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PATENT EXAMINER